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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,580	02/15/2001	Lawrence E. Cornett	023533-0113	4347

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 06/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/783,580	CORNETT ET AL.	
	Examiner	Art Unit	
	Scott Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-38 and 44-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-38 and 44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 5/8/02 has been entered. Claims 6, 7 and 39-43 have been cancelled. Claims 44-50 have been added.

As a result of this amendment, no restriction requirement is necessary. The telephonic request for election had been based on four inventions, Group I, claims 1-5 and 8-38, drawn to methods of producing a β2AR in human cells; Group II, claims 6-7, drawn to a host cell transfected with DNA encoding a β2AR; Group III, claim 30, drawn to a kit comprising a β2AR agonist and an agent that induces a promoter; and Group IV, claims 40-43, drawn to an *in vitro* method of evaluating the effect of compounds on mammalian cells transfected with a vector encoding a β2AR. All pending claims are limited to Group I.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 14, 44-48 and 50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 13 requires use of a mammalian cell specific promoter, claims 14 requires use of a mammalian cell specific promoter that is an epithelial cell specific promoter, endothelial cell specific promoter, or smooth muscle cell specific promoter, and new claims 44-48 and 50 require use of a generic epithelial, endothelial, or smooth muscle cell specific promoter.

These promoters are described only by their function - direct cell-specific transcription in certain types of cells. The specification provides no description of the structure of such promoters, i.e. their nucleotide sequences, and no evidence that the members of a class of such promoter share a common structure. Except for disclosing a prior art reference for a single species of epithelial specific promoter (page 20, lines 22-24), their is no evidence of record that such isolated promoters were well known in the prior art or to Applicant. While it is known that certain genes are expressed in a cell-type specific fashion, such knowledge does not constitute possession of the actual sequence responsible for the function. An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method

for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

This rejection *might be* overcome if evidence can be provided that shows, as general classes, isolated epithelial cell specific promoters, endothelial cell specific promoters, and smooth muscle cell specific promoters were sufficiently well known in the art at the time the invention was made that mere mention of the terms would constitute an adequate description of such classes of promoter to one of skill in the art, i.e. that disclosure in the instant specification of the actual structures of representative species would have been unnecessary.

With respect to the new claims 44-48 and 50, these claims introduce new matter into the specification. The specification, e.g. at page 20, lines 20-24, and original claim 14 describe epithelial cell specific promoters, endothelial cell specific promoters, and smooth muscle cell specific promoters that are *mammalian* promoters. Claims 44-48 and 50 are not limited to mammalian promoters, and thus exceed the original description of the cell specific promoters

originally contemplated by Applicant. This part of the rejection would be overcome by amending these claim limiting the promoters to mammalian cell specific promoters.

Claims 1-5, 8-38, and 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5, 44 and 45 are directed to a generic method of providing β2-adrenergic receptor (β2AR) to airway epithelial cells, blood vessel endothelial cells, or airway or blood vessel smooth muscle cells of a human subject by administering DNA encoding the receptor. Claims 30-32 and 46 are directed to pharmaceutical compositions comprising a DNA vector encoding the receptor. While these claims are not explicitly directed to any particular *in vivo* use the only asserted use in the specification is for treatment of any airway or vascular disease in a human, i.e. the specification does not teach any other use. Claims 8-29 and claims 33-38 and 47-50 are explicitly directed to a method of treating any airway or vascular disease in a human or a kit for use in such a method. Consequently, the invention as a whole is directed to either to a method of or products for gene therapy for any vascular or airway disease in a human.

35 USC 112, first paragraph requires that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). The instant

specification fails in this regard. While the claims are directed to treatment of any or all human airway and vascular diseases, the specification describes only two applications, to improve response to β2AR agonists for bronchodilation in treating airway diseases such as asthma where is needed, and to increase vascular dilation in pulmonary or systemic hypertension. The first is the only disclosed example of an airway disease that could be treated; the specification does not teach if or how this method would be used to treat other airway diseases, such as α1-antitrypsin deficiency, cystic fibrosis, black lung, or lung cancer. The second is application is the only disclosed example of a vascular disease that could be treated; the specification does not teach if or how this method would be used to treat other vascular diseases, such as atherosclerosis, congestive heart failure, stroke, hypotension. The specification appears to teach away from treating any other types of vascular disease in pointing out that vasodilators, such as β2AR agonists, cannot used to treat pulmonary hypertension because they cause systemic arterial dilation leading to circulatory shock and death. It follows therefor, that systemic treatment with the claimed method may have the same consequence, by systemically making arteries more sensitive to endogenous β2AR agonists. The specification (page 23) teaches that smooth muscle cells in pulmonary arteries are to be targeted, and that the arterial endothelium presents a tight diffusion barrier to viruses requiring "an appropriately designed gene therapy vector" to reach the targeted cells. However, the specification fails to teach what "an appropriately designed gene therapy vector" is for this application. The law under §112, first para. requires that the disclosure in the application shall inform those skilled in the art how to use the invention, *not* how to find

out for themselves how to use it. *In re Gardner,* 166 USPQ 138, 141 (CCPA 1970). In this case, treatment of diseases or conditions other than asthma is left to one skilled in the art to devise. The specification in essence is merely an invitation to identify other potential applications of the claimed method, and then develop them.

The specification provides detailed guidance on the construction of AAV vectors carrying a transgene encoding a β2AR and on methods to assess transfection parameters, such as transfection efficiency and physiological consequences of β2AR expression, with cultured cells and Norway rats. However, there is no indication that any such studies were performed, and no evidence of what level of transfection or physiological consequence could be expected in Norway rat, much less how such results would be extrapolated to treating human disease, to which the claims are limited. The specification does not disclose any actual working examples relevant to the claimed methods. All description of methods and the actual vectors are prophetic. The prophetic teachings constitute guidance only, not evidence of actual reduction to practice. Though not controlling, the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. *Ex parte Sudilovsky*, 21 USPQ2d 1702, 1705 (BPAI 1991); *In re Novak*, 134 USPQ 335 (CCPA 1962); *In re Fouche*, 169 USPQ 429 (CCPA 1971).

As indicated above, the claimed invention is directed to treatment of human disease by gene therapy. Orkin et al. (1995) is a review of the infant state of the art of gene therapy before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). Rosenberg et al. (Science 287: 1751, 2000) at the time the instant invention was made disclosed that "despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." They disclose that those skilled in the gene therapy art continued to express enthusiastic optimism for gene therapy, but such promise was unrealistic. Thus, up until the time the invention was made, the art of gene therapy was still undeveloped and highly unpredictable. These references show that merely because a particular gene therapy application is promising, is not an indication that it will be successful.

Factor (Mol. Ther. 4 (6): 515-524, 2001) reviews the development of potential gene therapy to treat acute diseases, such as asthma. Published well after the instant invention was made, it only suggests that asthma may be treatable by gene therapy, i.e. in the future (pages 517-518). It points out that there are expected difficulties to be overcome in treating asthma, such as transducing airway epithelial cells due to the location of their viral receptors, the polygenic nature of asthma, lack of consensus on its pathophysiology and physical barriers stemming from airway inflammation and injury. Demoly (Lung Biology in Health and Disease 136: 551-569, 1999), reviewing development of potential asthma gene therapy, concluded that choosing a gene to treat asthma and whether it would work "remains entirely speculative" (page 565). The instant specification does not address the difficulties of receptor location or the physical barriers resulting from the disease. In the absence of a working example, it is unpredictable whether simple administration of a vector by inhalation would allow effective transfection of airway epithelial cells or smooth muscle cells to produce any meaningful physiological effect. If it is not effective, then additional experimentation would be required to determine how to deliver the vector effectively.

With respect to liposome-mediated gene therapy (claims 10 and 12) , Factor discloses (page 515, col. 2) that the modest gene transfer suggests that plasmid-based therapies will be limited to instances where only a few cells need to be transduced, such as where the transgene encodes a secreted product. Demoly et al. in reviewing development of gene therapy for asthma teaches that plasmid-based, including liposomal, approaches were suitable only for DNA

vaccines. The instant specification does not indicate what level of transfection would be required in order to obtain a physiologically relevant effect, and β2AR is not a secreted protein, e.g. a cytokine or hormone. The specification provides no guidance on improving liposomal delivery of plasmids to the extent it would be successful in the claimed invention.

Claims 13, 14, 44-48 and 50 require use of a generic epithelial, endothelial, or smooth muscle cell specific promoter. The specification does not disclose any examples of such promoters, except one by improper incorporation to a journal article, nor does it teach how to make them. There is no evidence of record that such generic promoters were well known in the art.

In summary, the claims are much broader than the embodiments disclosed with any detail or guidance in the specification. The claimed invention is purely prophetic and is directed to subject matter that is highly unpredictable, and thus far largely unsuccessful. The guidance provided by the specification is mainly directed to determining whether the treatment of asthma, specifically, is feasible, rather than how to use it effectively without first having to engage in further research. Consequently, there is ample reason to doubt that the claimed invention could be practiced without further excessive and undue experimentation.

Claim Rejections - 35 USC § 102 & 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-34, and 37 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bertin et al. (Proc. Natl. Acad. Sci. USA 91: 8827-8831, 1994).

Bretin discloses a plasmid vector comprising a transgene encoding a fusion polypeptide, comprising a β2AR and an α subunit of adenylyl cyclase-stimulatory G protein, and operably linked to the CMV promoter, to be used with a β2AR agonist and cultured mammalian cells (page 8827, col. 2; page 8828, col. 2). The fusion polypeptide is a modified β2AR. Limitations on the intended use of the products claimed do not appear to imply any physical limitation not met by the prior art products.

Claims 30, 32, 33, and 37 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Kawahira et al. (J. Thorac. Cardiovasc. Surg. 118 (3): 446-451, Sep. 1999); and

claims 1, 4, 8-10, 12, 15, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawahira et al. (J. Thorac. Cardiovasc. Surg. 118 (3): 446-451, Sep. 1999).

Kawahira et al. teaches development of a method of providing β2AR globally to heart to enhance cardiac function by intracoronary infusion of HVJ liposome comprising a plasmid vector having a human β2AR coding sequence operably linked to a CMV promoter (which contains an enhancer). The infusion is followed by delivering a β2AR agonist. The reference demonstrates the procedure in rats and shows that it improves cardiac function in a transplanted heart in response to a β2AR agonist (see entire reference). The reference states that it should be possible to deliver the β2AR gene to humans being treated for cardiac arrest (a vascular disease) (page

450, col. 2). Although cardiomyocytes are the target in this method and the paper does not address transfection of endothelia or smooth muscle, the mode of delivery requires the vector to pass through vascular endothelia and smooth muscle, and consequently would be expected to transfect at least one cell of one of these tissues. Suitable for arterial delivery would also be suitable for intravenous delivery; the claims do not require that delivery be intravenous.

With respect to method claims 1, 4, 8-10, 12, 15, 19-22, it would have been obvious to one of skill in the art at the time the invention was made to have practiced the method on a human suffering from cardiac arrest with the method of Kawahira et al. as part of clinical investigation on methods for improving cardiac function in a failing human heart, e.g. clinical trials, given the explicit suggestion in the reference. The working example in the reference provides a reasonable expectation that the modest goal of transfecting and expressing β2AR in "at least one of said cells" would be obtained. The claims require no more result.

This rejection would be overcome by limiting claims to airway treatment (in the case of methods) and aerosol compositions for products.

Claims 30, 32, 33, and 37 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kawahira et al. (Circulation 98 (19): 262-268, 1998); and

claims 1, 4, 8-10, 12, 15, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawahira et al. (Circulation 98 (19): II-262 - II-268, 1998).

Kawahira et al. teaches development of a method of providing β2AR globally to heart to enhance cardiac function by intracoronary perfusion of HVJ liposome comprising a plasmid vector having a human β2AR coding sequence operably linked to a CMV promoter (which contains an enhancer). The infusion is followed by delivering a β2AR agonist. The reference demonstrates the procedure in rats and shows that it improves cardiac function in a failing heart in response to a β2AR agonist (see entire reference). The reference states that it should be possible to deliver the β2AR gene to humans being treated for cardiac arrest (a vascular disease) (page II-266, col. 1). Although cardiomyocytes are the target in this method and the paper does not address transfection of endothelia or smooth muscle, the mode of delivery requires the vector to pass through vascular endothelia and smooth muscle, and consequently would be expected to transfect at least one cell of one of these tissues. Suitable for arterial delivery would also be suitable for intravenous delivery; the claims do not require that delivery be intravenous.

With respect to method claims 1, 4, 8-10, 12, 15, 19-22, it would have been obvious to one of skill in the art at the time the invention was made to have practiced the method on a human suffering from cardiac arrest with the method of Kawahira et al. as part of clinical investigation on methods for improving cardiac function in a failing human heart, e.g. clinical trials, given the explicit suggestion in the reference. The working example in the reference provides a reasonable expectation that the modest goal of transfecting and expressing β2AR in "at least one of said cells" would be obtained. The claims require no more result.

This rejection would be overcome by limiting claims to airway treatment (in the case of methods) and aerosol compositions for products.

Claims 30, 32, 33, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Drazner et al. (J. Clin. Invest. 99: 288-296, 1997).

Drazner et al. discloses an adenoviral vector comprising coding for human human β2AR coding sequence operably linked to a CMV promoter (which contains an enhancer) (page 289) to be used in combination with a β2AR agonist (page 290, col. 1). Limitations on the intended use of the products claimed do not appear to imply any physical limitation not met by the prior art products.

Claims 1, 4, 8, 11, 15, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maurice et al. (J. Clin. Invest. 104: 21-29, July 1999) as evidenced by Drazner et al. (J. Clin. Invest. 99: 288-296, 1997).

Maurice et al. teaches development of a method of providing β2AR globally to heart to enhance cardiac function by intracoronary perfusion of an adenoviral vector having a human β2AR coding sequence operably linked to a CMV promoter (which contains an enhancer) (page 22, col. 1 citing Drazner et al., ref. 17). The infusion is followed by delivering a β2AR agonist. The reference demonstrates the procedure in rabbits and shows that it improves cardiac function in a failing heart in response to a β2AR agonist (see entire reference). The reference states that

the method may have potential for producing therapeutic cardiac inotropy in humans being treated for chronic heart failure (a vascular disease) (page 27, col. 1; page 28 , col. 2). Although cardiomyocytes are the target in this method and the paper does not address transfection of endothelia or smooth muscle, the mode of delivery requires the vector to pass through vascular endothelia and smooth muscle, and consequently would be expected to transfect at least one cell of one of these tissues. Vector composition suitable for arterial delivery would also be suitable for intravenous delivery; the claims do not require that delivery be intravenous.

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have practiced the method on a human suffering from cardiac arrest with the method of Maurice et al. as part of clinical investigation on methods for developing intracoronary artery delivery for global gene transfer to the human myocardium and for improving cardiac function in a failing human heart, e.g. clinical trials, given the explicit suggestion in the reference (see Discussion section). The working example in the reference provides a reasonable expectation that the modest goal of transfecting and expressing β2AR in "at least one of said cells" would be obtained. The claims require no more result.

This rejection would be overcome by limiting claims to airway treatment (in the case of methods) and aerosol compositions for products.

Claims 1, 3-5, 8, 10-13, 15-22, 30, 32, 33, 35, 37, 38 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (US 6,306,830) as evidenced by Ping et al.

(Microcirc. 3 (2): 225-228, 1996) in view of any one of Kawahira et al. (J. Thorac. Cardiovasc. Surg. 118 (3): 446-451, Sep. 1999); Kawahira et al. (Circulation 98 (19): 262-268, 1998); or Maurice et al. (J. Clin. Invest. 104: 21-29, July 1999).

Hammond et al. teaches a method of gene therapy for improving cardiac function in treatment of congestive heart failure in humans, comprising delivery of a vector comprising transgene encoding a β2AR *inter alia* to coronary blood vessels. The transgene is operably linked to an inducible promoter, a tissue specific promoter or a CMV promoter, which may optionally comprise a heterologous enhancer. The vector may be adenovirus or AAV vector or liposomes. See col. 5-7 for overview. (Ping et al. disclosed that both adenoviral and AAV vectors efficiently transfect cardiomyocytes and smooth muscle cells of the heart and that AAV transfection was more stable.) While the reference discloses using a β2AR transgene, other genes are described as being more preferred.

However, the two Kawahira et al. references and Maurice et al., which have been described above, disclosed similar methods using vectors to deliver a β2AR gene to the heart by similar methods to that of Hammond, and have shown that the subsequent expression of β2AR improves cardiac function in response to a β2AR agonist.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a β2AR gene in the method of Hammond to treat human congestive heart failure, as suggested by Hammond, with a reasonable expectation of success since each of the two Kawahira et al. references and Maurice et al. provide working examples

with animal models showing that the gene can be delivered globally to the heart, and results in improved cardiac function in response to β2AR agonist. Although cardiomyocytes are the target in this method and the reference do not address transfection of endothelia or smooth muscle, the mode of delivery requires the vector to pass through vascular endothelia and smooth muscle, and consequently would be expected to transfect at least one cell of one of these tissues, as evidenced by Ping et al. With respect to the use of inducible promoters, it is implicit that one would administer the inducer in order to effect expression of the transgene.

This rejection would be overcome by limiting claims to airway treatment (in the case of methods) and aerosol compositions for products.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER